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10/593,401	11/13/2006	Gerhard Muhrer	33696-US-PCT	2784

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,401	MUHRER ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/11/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/11/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the amendments and remarks filed on 11/11/10. Claims 7-8, 11-12 and 19 have been amended and claim 22 has been cancelled. New claim 23 has been added. Accordingly, claims **1-19 and 23** are pending and under examination on the merits.

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Drawings

The replacement drawings were received on 11/11/10. These drawings are entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeStefano et al (6,135,628).

DeStefano et al teach a method and apparatus for homogenizing aerosol formulations. Disclosed is a method and apparatus for homogenizing and micronizing aerosol formulations. The method includes the steps of homogenizing and micronizing an aerosol formulation at ambient temperature in a closed apparatus where the entire

apparatus is maintained under elevated pressure. The apparatus includes a closed loop containing a reaction vessel, a homogenizer and a fluid conduit interconnecting the reaction vessel and the homogenizer. The homogenizer includes an interaction chamber and an intensifier pump. The interaction chamber includes a stream splitter for separating a stream of aerosol formulation components into two streams and an impaction chamber for recombining the stream (see abstract).

DeStephano et al teach a closed, pressurizable system for homogenizing aerosol formulations including the following components: (1) A pressurizable mixing vessel having inlet and outlet means; (2) A homogenizer disposed in fluid communication with the reaction vessel, said homogenizer including a plurality of nozzles having elongated orifices to eject under pressure sheets of the liquid to be homogenized, said nozzles being arranged to effect turbulent jet interaction of said sheets along a common jet interaction front and said sheets being ejected by said nozzles into a low-pressure zone filled with said liquid of the sheets along a common liquid jet interaction front and said sheets being ejected by said nozzles into a low-pressure zone filled with said liquid further creating turbulent jet interaction along a common boundary essentially defined and formed by said mixture in said low pressure zone and by said sheets ejected into said low pressure zone; jet interaction chamber-defining means arranged to provide said low pressure zone of said liquid system in which said turbulent jet interaction is effected; pump means for delivering said liquid system under pressure to said nozzles; and (3) fluid conduits running from said outlet of said mixing vessel to the homogenizer

and from the homogenizer back to the inlet of the mixing vessel, to form a closed apparatus therebetween.

The present invention is also directed to a method for homogenizing an aerosol formulation in a closed continuous-loop system under elevated pressure, the method including the steps of determining a desired level of homogenization, mixing an aerosol formulation in a mixing vessel, circulating the mixed aerosol formulation through a high pressure homogenizer, operating the high pressure homogenizer at a pressure sufficient to achieve homogenization of the mixed aerosol formulation, circulating the aerosol formulation back into the mixing vessel and repeating the aforementioned steps until the desired level of homogenization is achieved.

The closed continuous loop system may be connected by connecting means and conduit means to a high pressure filling station to fill aerosol containers. In an alternative embodiment, the closed continuous loop system may be used to prepare a concentrated aerosol formulation which is transferred by connecting means and conduit means to a large vessel where it is diluted with the aerosol propellant to a predetermined volume of aerosol formulation. Accordingly, the objects of the disclosure are to provide: -an improved method and system for homogenizing volatile mixtures,

- a method and system for homogenizing volatile mixtures, such as aerosol formulations comprising low boiling HFA propellants, at ambient temperature,

- a method and system which permit the preparation of aerosol formulations comprising a wide range of surfactants, including those surfactants which would not be miscible in the formulation if processed at reduced temperature,

And to provide a method and system which can both micronize particles of active substance in an aerosol formulation and homogenize the formulation, eliminating the need for prior milling of the active substance (see col. 4, lines 9-35).

DeStefano et al also teach the device which includes a high pressure homogenizer 12 that operates upon an aerosol formulation at a pressure sufficient to achieve homogenization and, where applicable and desired, the simultaneous micronization of solid particles present in the aerosol formulation. The high pressure homogenizer 12 may be, for example, a Microfluidics Model M-110F Microfluidizer® (see col. 5, lines 22-65).

DeStefano et al teach that the active ingredient may include for example, a pharmaceutically effective amount of a pharmaceutically active respiratory compound. Active ingredients include, for example, ipratropium bromide and albuterol sulfate. Possible surfactants include, for example, perfluorocarboxylic acid, polyethyleneglycols, polyethylene oxide sorbitan fatty acid ester, sorbitan esters, such as sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, and the like, polyvinylpyrrolidone, propylene glycol and oleic acid. A propellant is supplied to the reaction vessel 10, under pressure, through a valved inlet 11. The propellant may be, for example, a low boiling hydrocarbon; an HFA propellant such as HFA-227, HFA-134a or a combination of HFA-227 and HFA-134a; or a CFC propellant such as CFC 12 or 114, or a mixture thereof. The propellant may additionally comprise a solvent, such as for example an alcohol such as ethanol (see col. 6, lines 26-56).

DeStefano et al disclose that while carrying out the process of homogenization, or simultaneous homogenization and micronization, aerosol formulation flows through the components of the embodiment shown in FIG. 2 in the following sequence: starting from the mixing vessel 10, the formulation flows through the drain valve 50, conduit 30(c), the three-way valve 100, conduit 30(d), the high pressure homogenizer 12, the conduit 30(e), the three-way valve 101, conduit 30(f), the optionally present flow meter 170, conduit 30(i), by-pass connector 110, open by-pass valve 90, conduit 30(n), the optionally present flow meter 171, conduit 30(o), and then back into the mixing vessel 10. Once homogenization and, if applicable, micronization is complete, the flow of formulation is diverted from the homogenizer 12, to the pump 70, by way of conduit 30(g) and conduit 30(h), by operation of the three-way valves 100 and 101. The high pressure homogenizer 12 is removed from the circulation path of the aerosol formulation to avoid over-processing of the aerosol formulation. Up to this point the pump of high pressure homogenizer 12 is responsible for the circulation of formulation through the apparatus. Once the flow of formulation is diverted from the high pressure homogenizer 12, the pump 70 takes over this task. The pump 70, as well as the stirrer 40 of the reaction vessel 10, impart sufficient agitation to maintain suspension. Preferably, after about 15 minutes of circulation by the pump 70, when both the temperature and the pressure within the vessel increase to values which are close to their starting values, dispensing may begin (see col. 9, lines 10-40).

While DeStefano et al does not anticipate the instant claims, it discloses every limitation and sufficient teachings to one of ordinary skill in the art to make and use the invention as claimed. DeStefano et al teach the process of micronization by way of high pressure homogenization while employing excipients such as surfactants to prepare suitable compositions for pulmonary delivery of active agents. "[w]hen an application simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a patent application claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an automaton." Id. at 1742. Consistent with this reasoning, it would have been obvious to have selected specific steps and components of the prior art disclosure, to arrive at a process "yielding no more than one would expect from such an arrangement".

Claims 1-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (6,228,346) in view of Bernini et al (WO 0025746).

Zhang et al teach that propellant gases with a low evaporation enthalpy, such as carbon dioxide, sulfur hexafluoride and ethane, can be used in the subcritical state in a pharmaceutical aerosol, without entailing the aforementioned disadvantages, if they are mixed with another gas that has a high evaporation enthalpy and a low vapor pressure, such as butane, propane or dimethyl ether. The added gas has two functions: to decrease the overall system's vapor pressure and to increase the system's dissolving capacity. The system's evaporation enthalpy is still sufficiently small, with the result that problems do not arise during evaporation. Due to the presence of non-inflammable gas, the system's inflammability is also substantially reduced. A special propellant mixture is prepared for pharmaceutical aerosols so as to micronize the drugs for pulmonary application. This propellant mixture is present in the subcritical state and contains at least one component from a first class of propellant gases and at least one component from a second class of propellant gases, with different enthalpy and vapor pressures (see summary).

Zhnag et al teach a pharmaceutical aerosol for pulmonary application; in addition to one or more pharmaceutical substances, this aerosol contains: 1) a propellant mixture in an amount of from 10 to 80 wt. %, and wherein the pharmaceutical may be present in the aerosol composition in a dissolved state (solution aerosol) or in a suspended state (suspension aerosol); 2) A drug; 3) A surfactant which is frequently

added in a suspension aerosol for enhanced suspension of the pharmaceutical. A suspension aerosol formulation requires the surfactant used to be soluble in the propellant mixture. The conventional surfactants, such as oleic acid, lecithin and sorbitan trioleate, are easily soluble in the 2nd propellant gas class and are also soluble in the propellant gas mixture used here. In consequence, such surfactants can be used without difficulty in the production of a suspension aerosol formulation.

The process produces particles generated by spraying, having a diameter of less than 8 µm, and preferably, the particle size is less than 5 µm. The percentages each relate to the total mass of the produced pharmaceutical particles "dried" after evaporating the propellant. These particles therefore have a smaller mass and are not so easily precipitated in the mouthpiece of the metered dose aerosol or in the spacer. Improved respirability means that not only the bronchial or upper pulmonary region, but also more deeply lying sections of the lungs and pulmonary alveoli are reached. This is not only a decisive advantage when the lung itself represents the affected organ to be treated, the resorption of systemic-action pharmaceuticals is also improved (see col. 4).

Zhang et al also teach that the compositions may contain other common, pharmaceutically compatible diluents, excipients, entrainers, solubilizers and surfactants. The pharmaceutical may be present in the aerosol composition as a solution or suspension with a percentage content of 0.01 to 5 wt. %, preferably 0.03 to 1 wt. %. The operating pressure of the composition is 2 to 100, preferably 3 to 50 bar, with particular preference for 5 to 20 bar. For micronization, a spray nozzle common for this purpose is used. In a preferred embodiment of the newly developed pharmaceutical

aerosol, the propellant mixture solely comprises one or more components from the above two classes. The aforementioned solubilizers and/or surfactants can also be optionally present. To achieve specific or improved effects, a combination of different active ingredients with varying percentage contents can be used in an aerosol formulation, e.g. combinations of ipratropium bromide and fenoterol, salbutamol and disodium cromoglicinic acid, and salbutamol and beclometason-17,21-dipropionate (see col. 5).

Zhang et al teach a device that comprises a gas cylinder, a high-pressure pump, a safety valve, a check valve, a spray nozzle, and an autoclave. The high-pressure pump is used to pump dimethyl ether, propane or butane out of the cylinder, which is positioned on a balance, into the autoclave. The feed quantity can be read off from the balance. After the pressure in the autoclave has reached the desired value, it is agitated for about 90 minutes. It is then not moved for 30 minutes, causing all the undissolved substances to separate from the gas mixture. A high-pressure viewing cell with a 35 ml volume is used to evaluate the stability of a suspension. The viewing cell has a large viewing diameter of 30 mm, making it much easier to observe the suspension conventional nozzles are used to process aerosols (see col. 5, line 59 to col. 6. line 30). The suitable nozzle aperture of a spray nozzle depends on the operating pressure (see col. 8, lines 34-37). Process of preparing particles is also exemplified in Examples 1-9. Zhang et al discloses employing a high pressure pump in the process, but lacks specific disclosure on the step of high pressure homogenization. However, this deficiency is cured by Bernini et al.

Bernini et al a process for the preparation of suspensions of drug particles for inhalation delivery. The process includes the step of homogenising and micronising the formulation in a turboemulsifier provided with a high-potency turbine, optionally followed by a treatment in a high pressure homogenizer (see abstract). The high pressure homogenization reduces the mean size of the suspended particles. A typical apparatus used for this treatment, such as the Microfluidizer®, includes a high pressure pump which can supply pressures up to 1500 bar and one or more interaction chambers (see page 3, lines 12-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have implemented the step of high pressure homogenization of Bernini et al in the processes and formulations of Zhang et al with a reasonable expectation of successfully preparing dry powder particles in a suitable particle size with the known process of high pressure homogenization. In other words, the claims would have been obvious because the technique for improving a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 11/11/10 have been fully considered but they are not persuasive.

Applicants main argument is that the prior art references, DeStefano and Zhang et al do not teach suspending the active agent in a gas propellant or compressed gas.

Applicant argues that “DeStefano fails to teach or suggest each and every element of the presently claimed invention, and the Examiner has failed to point to any reason for the person of ordinary skill in the art to modify the reference to provide for the missing elements. Accordingly, the reference cannot be found to render the claims obvious. In particular, DeStefano fails to teach or suggest a micronization method in which a pharmaceutically active agent is suspended n a gas propellant or compressed gas”.

Applicants add that “DeStefano is directed to the use of liquid propellants for suspending/dissolving pharmaceutical agents as an aerosol formulation. ……Hence, whenever DeStefano mentions "aerosol formulation" it is a reference to the liquid, not gaseous, form of the composition” (see remarks pages 9-10).

With regards to the rejection claims over Zhang et al in view of Bernini et al, Applicant similarly argues that Zhang et al teaches a propellant mixture for micronization, where the propellant mixture is present in the subcritical state..” (see Remarks, page 11). Applicant continues that “Like DeStefano above, Zhang is direct to suspension of the pharmaceutically active agent in a liquid medium to prepare the aerosol formulations” (see Remarks, page 11, Last two lines).

The above arguments are not persuasive for the following reasons. 1) In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a gaseous state) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims require that the active agent being suspended in a gas propellant. The claims do not require that the suspension be in a gaseous state. Both DeStefano and Zhang et al references teach active agents being suspended in a liquefied gas propellant, e.g. HFA or carbon dioxide. The instant claims also employ the open-ended transitional term "comprising' which allows for the presence of non recited components or features.

2) Even if the claims are amended to recite that the active agents are suspended in a gas propellant and are in gaseous state, it would have been obvious to one of ordinary skill in the art to have modified the references by substituting the liquefied gas propellant with a gaseous gas propellant because the options would have been very finite and it would have been obvious for one of ordinary skill in the art to have tested the same process with a second option. It has been held that "In determining obviousness, neither the particular motivation to make the claimed invention nor the problem the inventor is solving controls. The proper analysis is whether the claimed invention **would have been obvious** to one of ordinary skill in the art after consideration of all the facts." MPEP 2141.

Additionally, it has been held that "The arguments of counsel cannot take the place of evidence in the record." *In re Schulze,* 346 F.2d 600, 145 USPW 716, 718 (CCPA 1965), *In re Huang*, 40 USPQ 2d 1685 (Fed. Cir. 1996), *In re De Blauwe et al.*, 222 USPQ 191, (Fed. Cir. 1984). Applicant has not proved any factual evidence establishing unobviousness. Applicant only argues that it would not have been obvious to one of ordinary skill to prepare the formulations as claimed.

3) Even if the claims are amended to recite that the active agents are suspended in a gas propellant and are in gaseous state, the prior art references would still meet the claimed invention because the end result in this process is the micronized dry powder comprising the active agent. Regardless of the specific steps in a process, if it has been shown that the same product has been made, the modifications to the steps would not be considered patentable. Unless Applicant demonstrates the criticality of the order of addition and that the prior art is not the same product as the instant application, changes in sequence of adding ingredients has been rendered to be *prima facie* obvious Note MPEP 2144.04 [R-1]. *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930).

Claims 1-19 and 23 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

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